I. SCIENTIFIC ABSTRACT:

The incidence of squamous cell carcinoma of the upper aerodigestive tract is approximately 42,800 cases per year in the United States with worldwide projections of more than 500,000 annually (1). Oral cavity and oral pharyngeal tumors comprise the vast majority of these cases which are among the most morbid of human cancers. Present therapy includes deforming radical surgical procedures coupled with radiotherapy and possibly chemotherapy. Aside from the severe cosmetic deformity, surgical resection frequently results in significant functional deficits in speech, swallowing, and upper extremity strength. Radiotherapy also brings substantial morbidity with mandible and laryngeal cartilage radionecrosis, soft tissue fibrosis and mucosal atrophy, pain, and xerostomia (2). There are a wide variety of chemotherapy regimens for head and neck squamous cell cancer with the most common being single or combination treatment with Cisplatin, 5-Fluorouracil, or Methotrexate. Chemotherapy regimens, however, are not innocuous and frequent complications from their use include variable degrees of gastrointestinal, bone marrow, and renal toxicity (2). Furthermore, the efficacy of adjuvant or induction chemotherapy in head and neck cancer remains questionable with no clinical trial to date demonstrating improved survival (1). Despite many years of studying squamous cell cancer, the present therapies can rarely hope to provide two year survival in more than 30% in patients with advanced stage III and IV disease (1,3).

Direct introduction of therapeutic genes into malignant cells in vivo may provide an effective treatment of solid tumors including tumors of the head and neck. Of these strategies, conferring drug sensitivity holds the greatest promise for clinical application in the near future. The gene coding for the herpes simplex virus thymidine kinase (HSV-tk) enzyme is the leading therapeutic gene. Thymidine kinase phosphorylates the nucleoside analog ganciclovir (GCV) into a phosphorylated intermediate that is incorporated into newly-synthesized DNA of dividing cells. The incorporated analog hinders further DNA replication leading to the cell's death. Since normal mammalian cells do not possess this enzyme, cytotoxicity depends on the successful introduction and expression of the HSV-tk gene, phosphorylation of ganciclovir, and synthesis of DNA. Non-dividing cells may express HSV-tk and phosphorylate ganciclovir but are not harmed since they do not synthesize DNA. This approach is especially suitable for the treatment of head and neck tumors where rapidly dividing tumor cells invade adjacent tissues made up largely of non-proliferating cells. Several techniques have been used to introduce therapeutic genes into tumors. Of these, viral transduction is currently the most efficient method. Vectors based upon retrovirus, herpes virus and adenovirus are the most common gene therapy. The adenovirus-based vectors have advantages over the other virus vectors that make them leading candidates for somatic gene therapy. We have demonstrated using a head and neck cancer animal models that adenovirus-mediated transfer of the HSV-tk gene and GCV treatment resulted in ablation of the tumors and significant increases in life spans.

This phase I study is designed to study the safety and efficacy of gene therapy for patients with head and neck tumors. Patients with tumors refractory to all potentially curative therapy will be treated with direct intra-tumor injections of replication-defective adenovirus vector delivering the HSV thymidine kinase gene. Initial tests will use $1x10^8$ (5×10^6 pfu). Ganciclovir will then be administered intravenously at 10 mg/kg/day for 7 days. Only one course of therapy will be administered. Each patient will be carefully monitored for one month for cytopathic or toxic effects by several methods including CT scans. Five patients will be tested with this low dose before another group of patients are treated with 5×10^8 ($2.5x\ 10^7$ pfu) and monitored closely for 1 month. This will be repeated until the target dose of $1x10^{10}$ (5×10^8 pfu) is reached or significant toxicity is detected. Effectiveness will be monitored by clinical exam and/or CT scans. The primary objective of this initial study is to determine whether the treatment is associated with significant toxicity.